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学位論文の題名	Genetic variation in the ATP binding cassette transporter ABCC10 is associated with neutropenia for docetaxel in Japanese lung cancer patients cohort （日本人肺癌患者において ABC 結合カセット輸送体 ABCC10 の遺伝子多型はドセタキセルの好中球減少と関連する） BMC Cancer 2019;19(1):246. doi: 10.1186/s12885-019-5438-2. PMID: 30890141
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Background: Docetaxel is a widely used cytotoxic agent for treatments of various cancers. The ATP binding cassette (ABC) transporter / multidrug resistance protein (MRP) ABCC10/MRP7, involved in transporting taxanes, has been associated with resistance to these agents. Furthermore, drug transporters influence anti-cancer pharmacokinetics, resulting in chemotherapy-induced adverse effects, such as neutropenia. Since genetic variation in drug transporters may affect clinical outcomes, we examined whether polymorphism of ABCC10 could affect clinical responses to docetaxel.

Methods: Using 18 NSCLC cell lines and CRISPR-based genome-edited HeLa cells, we analyzed whether genetic variants of ABCC10 (rs2125739, rs9349256) affected cytotoxicity to docetaxel. Subsequently, we analyzed genetic variants [ABCC10 (rs2125739), ABCB1 (C1236T, C3435T, G2677 T/A), ABCC2 (rs12762549), and SLCO1B3 (rs11045585)] in 69 blood samples of NSCLC patients treated with docetaxel monotherapy. Clinical outcomes were evaluated between genotype groups.

Results: In the cell lines, only one genetic variant (rs2125739) was significantly associated with docetaxel cytotoxicity, and this was confirmed in the genome-edited cell line. In the 69 NSCLC patients, there were no significant differences related to rs2125739 genotype in terms of RR, PFS, or OS. However, this SNP was associated with grade 3/4 neutropenia (T/C group 60% vs. T/T group 87%; P = 0.028). Furthermore, no patient with a T/C genotype experienced febrile neutropenia.

Conclusions: Our results indicate that genetic variation in the ABCC10 gene is associated with neutropenia for docetaxel treatment.